

517,416

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
31 December 2003 (31.12.2003)

PCT

(10) International Publication Number
WO 2004/000814 A1

(51) International Patent Classification⁷: **C07D 215/04**,
215/12, 409/10, 407/10, 401/10, 413/10, 413/14, 471/04,
401/04, 403/10, 417/10, A61K 31/4709, 31/47, 31/497,
A61P 29/00

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(21) International Application Number:
PCT/CA2003/000957

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,
CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK,
LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX,
MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD,
SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US,
UZ, VC, VN, YU, ZA, ZM, ZW.

(22) International Filing Date: 23 June 2003 (23.06.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/391,364 25 June 2002 (25.06.2002) US
60/428,313 22 November 2002 (22.11.2002) US

(84) Designated States (*regional*): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),
Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE,
ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO,
SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM,
GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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Published:
— *with international search report*

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*For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.*

(54) Title: 8-(BIARYL) QUINOLINE PDE4 INHIBITORS

(57) Abstract: 8-(biaryl) quinolines wherein the bi-aryl group at the 8-position is in a *meta* relationship to the quinoline group, are PDE4 inhibitors useful in the treatment of asthma, chronic bronchitis, chronic obstructive pulmonary disease, eosinophilic granuloma, psoriasis and other benign or malignant proliferative skin diseases, endotoxic shock, laminitis in horses, colic in horses, septic shock, ulcerative colitis, Crohn's disease, reperfusion injury of the myocardium and brain, inflammatory arthritis, chronic glomerulonephritis, atopic dermatitis, urticaria, adult respiratory distress syndrome, chronic obstructive pulmonary disease in animals, diabetes insipidus, allergic rhinitis, allergic conjunctivitis, vernal conjunctivitis, arterial restenosis, orthrosclerosis, atherosclerosis, neurogenic inflammation, pain, cough, rheumatoid arthritis, ankylosing spondylitis, transplant rejection, graft versus host disease, hypersecretion of gastric acid, bacterial, fungal induced sepsis, viral induced sepsis, fungal induced septic shock, viral induced septic shock, inflammation-mediated chronic tissue degeneration, cytokine-mediated chronic tissue degeneration, osteoarthritis, cancer, cachexia, muscle wasting, depression, memory impairment, tumour growth, or cancerous invasion of normal tissues. In another aspect, the present invention is directed to a method of enhancing cognition in a healthy subject comprising administering a safe cognition enhancing amount of phosphodiesterase-4 inhibitor. In particular, this invention is directed to a method of enhancing memory, learning, retention, recall, awareness and judgement in health subjects comprising administering a safe and cognition enhancing amount of a phosphodiesterase-4 inhibitor.

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/CA 03/00957

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D215/04 C07D215/12 C07D409/10 C07D407/10 C07D401/10
 C07D413/10 C07D413/14 C07D471/04 C07D401/04 C07D403/10
 C07D417/10 A61K31/4709 A61K31/47 A61K31/497 A61P29/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal; WPI Data, PAJ, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5 455 252 A (WILHELM ET. AL.) 3 October 1995 (1995-10-03) column 14, line 25 - line 46; claims; examples	1-35
Y	US 5 530 005 A (WILHELM ET. AL.) 25 June 1996 (1996-06-25) column 13, line 35 - line 53; claims; examples	1-35
P, Y	WO 02 094823 A (MERCK FROSST CANADA) 28 November 2002 (2002-11-28) page 1, line 5 - page 4, line 16; claims; examples	1-35
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☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
 "E" earlier document but published on or after the international filing date
 "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
 "O" document referring to an oral disclosure, use, exhibition or other means
 "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search

16 September 2003

Date of mailing of the international search report

29/09/2003

Name and mailing address of the ISA

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INTERNATIONAL SEARCH REPORT

International Application No.

PCT/ISA 03/00957

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 6 069 151 A (DYKE ET. AL.) 30 May 2000 (2000-05-30) column 4, line 66 -column 5, line 23; claims; examples	1-35
A	D. MACDONALD ET. AL.: "Hunting the Emesis and Efficacy targets of PDE4 Inhibitors. Identification of the Photoaffinity Probe 8-(3-Azidophenyl)-6-(4-Iodo-1H-1-imidazol yl)methylquinoline (APIIMQ)" JOURNAL OF MEDICINAL CHEMISTRY, vol. 43, no. 21, 30 September 2000 (2000-09-30), pages 3820-3, XP002254693 table 1	1-35

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA 03/00957

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 25-31 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/SA 03/00957

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 5455252	A	03-10-1995	AT 170855 T	15-09-1998
			AU 679222 B2	26-06-1997
			AU 6412994 A	24-10-1994
			CA 2159603 A1	13-10-1994
			DE 69413215 D1	15-10-1998
			DE 69413215 T2	28-01-1999
			DK 691966 T3	08-02-1999
			EP 0691966 A1	17-01-1996
			ES 2120028 T3	16-10-1998
			FI 954651 A	29-09-1995
			HU 9500111 A3	28-06-1995
			HU 73181 A2	28-06-1996
			JP 8511238 T	26-11-1996
			NO 953879 A	22-11-1995
			NZ 263436 A	22-08-1997
			WO 9422852 A1	13-10-1994
US 5530005	A	25-06-1996	US 5475003 A	12-12-1995
WO 02094823	A	28-11-2002	WO 02094823 A1	28-11-2002
			US 2003096829 A1	22-05-2003
US 6069151	A	30-05-2000	AT 246184 T	15-08-2003
			AU 711587 B2	14-10-1999
			AU 4875897 A	29-05-1998
			DE 69723863 D1	04-09-2003
			EP 0946541 A1	06-10-1999
			WO 9820007 A1	14-05-1998
			JP 2001503756 T	21-03-2001
			ZA 9710000 A	06-11-1998
			AU 735573 B2	12-07-2001
			AU 8222898 A	04-01-1999
			CN 1260784 T	19-07-2000
			EP 0993449 A1	19-04-2000
			WO 9857936 A1	23-12-1998
			JP 2002504925 T	12-02-2002
			ZA 9805253 A	17-06-1999